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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,857	12/07/2005	Mark E. Fraley	21405YP	1561

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
LOEWE, SUN JAE Y	

ART UNIT	PAPER NUMBER
1609	

MAIL DATE	DELIVERY MODE
06/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,857	FRALEY ET AL.	
	Examiner	Art Unit	
	Sun Jae Y. Loewe	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6 and 7* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received:

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

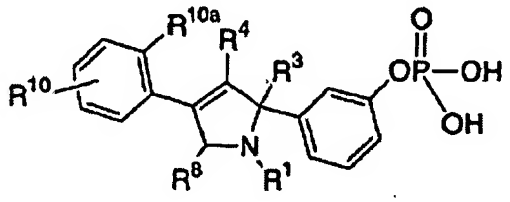
1. Applicant's election with traverse of Group I, and 3-{(2S)-4-(2,5-difluorophenyl)-1-[(dimethylamino)carbonyl]-2,5-dihydro-1H-pyrrol-2-yl}phenyl dihydrogen phosphate, in the reply filed on June 4, 2007 is acknowledged. The traversal is on the ground(s) that: (i) a special technical feature exists because the genus of compounds claimed incorporate at least one phosphate moiety (this feature distinguishes the instantly claimed compounds from being merely pyrrolidine derivatives); and (ii) there would be no serious burden to search the inventions set forth in Groups I and II. The restriction requirement was thus stated to be improper. This is not found persuasive for the following two reasons.

First, it is noted that compounds of independent claim 1 have in common a core structure defined only by a 5-membered nitrogen heterocycle, as the other structural limitations are defined as *variables* (R_1-R_9). Thus, the special technical feature linking the claims is a 5-membered nitrogen heterocycle which, as was previously shown in the restriction requirement dated May 16, 2007, is taught in the prior art (page 2).

Second, because the instant case is a national stage application submitted under 35 U.S.C. 371, the Unity of Invention practice in MPEP § 1850 and MPEP § 1893.03(d) was followed, not restriction practice. Thus, the criteria for burden stated in MPEP § 803 for national applications filed under 35 U.S.C. 111(a) does not apply (see also MPEP § 801).

The restriction requirement mailed on May 16, 2007 is still deemed proper and is made FINAL.

2. Based on Applicant's species election, the search and examination was performed for a the core structure defined in claim 4 (below) with the following additional structural limitations: R_{10}/R_{10a}=halo or alkyl; R_1=(C=O)$C_{1\text{-}10}$ alkyl (optionally substituted with OH, alkyl, or C_3 cycloalkyl) or (C=O)NR_cR_c'. Variables R_c, $R_{c'}$, R_3, R_4 and R_8 were examined relative to the full scope defined in claim 4. Compounds that do not meet these structural limitations are deemed to be patentably distinct.



IV

Furthermore, two additional compounds listed in claim 5 but not encompassed by this subgenus were also included in the search and examination:

2-(phosphonooxy)ethyl (1S)-1-{[(2S)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrol-1-yl]carbonyl}-2,2-dimethylpropylcarbamate; and

(1S)-1-cyclopropyl-2-[(2S)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1*H*-pyrrol-1-yl]-2-oxoethyl dihydrogen phosphate;

MPEP 1893.03(d) states that when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. The genus above was not allowable under 35 U.S.C 112 (see below sections 5 and 6). Thus, nonelected subject matter was *not* rejoined.

3. Claims 8-11 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on June 4, 2007.

Claim Objections

4. Claims 1-4, 6 and 7 are objected to for containing non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6 and 7 are rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically states that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the

description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. *Scope of Claims* (based on ***elected*** subject matter)

Claims 1-4, 6 and 7

Compounds of the generic formula shown in section 2, that are ester prodrugs of dihydropyrrole derivatives (specification page 2). The variables to the core structure are broadly defined, for example R_c and R_c' defined to encompass aryl, heterocyclyl, or the variables are optionally joined to form a monocyclic or bicyclic heterocyle comprising one or two additional heteroatoms and optionally further substituted with aryl, heterocycle (non-exhaustive definition). Further, variables like R_3, R_4 and R_8 can be optionally substituted with any substituent including for example, those noted for R_c and R_c' as well as additional phosphate groups.

II. *Scope of Disclosure*

Reduction to Practice: disclosure supports claim to following substituents

R_c and R_c'	alkyl optionally substituted OH tetrahydrofuran
$R_3/R_4/R_8$	H or unsubstituted alkyl

Reduction to Structural or Chemical Formulas:

It is noted that the disclosure *lists* possible substituents for all the variables in Markush style. However, this type of disclosure is not viewed to be a representation of any of the species it entails. A"laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Thus, there is no disclosure by reduction to structural/chemical formulas of species in addition to those reduced to practice.

Correlation between Structure and Function:

No correlation between structure and function is provided in the disclosure. Thus, it is not known what *specific structural elements*, shared by the genus of compounds claimed, are *essential* for the operability of the compounds as prodrugs. The extent of the art recognized correlation between structure and activity for this class of prodrugs is disclosed by Garbaccio et al. (eg. see page 1783), whose study is limited to two of the five species claimed (and supported for) in the instant specification: example 8-2 (specification p. 86) and example 9-3 (specification p. 89).

III. *Analysis of Fulfillment of Written Description Requirement:*

In the absence of a correlation between activity and structure, either disclosed or known in the art, it is not possible to predict what structural modifications will allow for the preservation of the desired activity. Thus, one of ordinary skill would not have a reasonable expectation that the compounds *not exemplified* in the disclosure, which differ *significantly* from the subgenus exemplified, would function as prodrugs of the dihydropyrrole derivatives. For instance, it is not possible to predict by structure alone, parameters such as rate of conversion to parent in vivo, clearance mechanism other than conversion to parent – both of which are relevant to the functionality of a compound as prodrug (eg. see Garbaccio et al., p. 1783, 1st column).

In conclusion:

(i) Substantial structural variation in the genus embraced by the claims

(ii) Disclosure of species supporting genus is limited to compounds reduced to practice; disclosure not commensurate in scope with genus claimed

(iii) Common structural attributes of the claimed genus (commensurate with scope of claims), combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Allowable Subject Matter

6. Claim 5 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

The compounds in claim 5 are allowable over the art of record. There are no compounds of the dihydropyrrole derivatives that anticipate or make obvious the instant claims because of the structural limitation that a $-OPO(OH)_2$ substituent be present in the structure.

Conclusions

7. No claims are allowed.

8. Any inquiry concerning this communication should be directed to Sun Jae Y. Loewe whose telephone number is 571-272-9074. The examiner can normally be reached on Monday through Friday from 7:30 am to 5:00 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Cecilia Tsang (571) 272-0562, can be reached. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sun Jae Y. Loewe, Ph.D.
Patent Examiner
Art Unit 1609, Group 1609
Technology Center 1600

CECILIA TSANG
SUPERVISORY PATENT EXAMINER